



RESEARCH ARTICLE

**REVISED** Adult attention-deficit/hyperactivity disorder:

**Associations between subtype and lifetime substance use – a clinical study [version 2; referees: 2 approved, 1 approved with reservations]**

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**Abstract**

ADHD is the one of the most prevalent childhood disorders and has been associated with impairments persisting into adulthood. Specifically, childhood ADHD is an independent clinical risk factor for the development of later substance use disorders (SUD). Moreover, adults who meet diagnostic criteria for ADHD have shown high rates of comorbid SUDs. Few studies, however, have reported on the relationship between ADHD subtypes and SUD in adult samples. The purpose of this study was to characterize a clinical sample of adults with ADHD and to identify possible associations between ADHD subtypes, lifetime substance use, and if ADHD subtypes may be preferentially associated with specific substances of abuse. We recruited 413 adult ADHD patients, performed an evaluation of their ADHD and conducted an interview on their use of psychotropic substances. Complete data was obtained for 349 patients. Lifetime substance abuse or dependence was 26% and occasional use was 57% in this sample. The inattentive subtype was significantly less likely to abuse or be dependent on cocaine than the combined subtype. Our findings underscore the high rate of comorbidity between substance use and ADHD in adults. The more frequent abuse/dependence of cocaine by adult patients with hyperactive-impulsive symptoms should be kept in mind when treating this patient group.

**Open Peer Review**

Referee Status: ✓ ? ✓

	Invited Referees		
	1	2	3
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**REVISED Amendments from Version 1**

We would like to thank the reviewers for their comments on this manuscript, which has been edited to address their feedback concerning the following points: In the Methods section of the paper the assessment of ADHD subtype (I) substance use (II) and comorbidities (III) was clarified; the Discussion section has been expanded to describe (IV) neurobiological findings among ADHD patients with a comorbid cocaine dependence and (V) to discuss more thoroughly limitations of this study, especially in regards to co-occurring personality disorders (VI). The conclusion section now includes a more detailed description of findings among patients with ADHD and a comorbid cocaine dependence receiving methylphenidate, in an effort to comment on the relevance of the presented findings for therapeutic approaches (VII). Additionally the references have been updated (VIII).

See referee reports

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a complex neuropsychiatric syndrome that is common not only in childhood and adolescence, but in adulthood<sup>1-4</sup>. It is characterized by symptoms of inattention (distractibility), hyperactivity, and impulsivity, which all contribute to significant psychosocial impairment in affected individuals of all age groups<sup>5-7</sup>. In order to make a diagnosis of ADHD, the two diagnostic manuals, the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders Third Edition Revision (DSM-III-R) and the World Health Organisation's (WHO) International Statistical Classification of Diseases and Related Health Conditions (ICD-10), require the presence of both inattentive and hyperactive-impulsive symptoms<sup>8,9</sup>.

In 1994, the introduction of the DSM Fourth Edition (IV)<sup>10</sup> marked a diversion from this route by allowing for a diagnosis of ADHD when either hyperactive-impulsive *or* inattentive behaviors were present, and thereby defined three subtypes of ADHD: a) a predominantly inattentive type, b) a predominantly hyperactive-impulsive type, and c) a combined type<sup>11</sup>. The following years saw a significant amount of research in which the importance of these subtypes in a clinical and epidemiological context was debated. For example, the clinical response to pharmacologic treatment by subtype or symptom clusters was investigated<sup>12-14</sup>, as were subtype differences in psychosocial functioning<sup>15,16</sup>, and the rate of comorbidity<sup>17</sup> in different age groups.

In both pediatric and adult populations, ADHD is significantly comorbid with a wide range of other DSM-IV disorders, irrespective of subtype. The most prevalent of these are mood, anxiety, impulse control, and substance use disorders (SUD)<sup>18-20</sup>. Data that stem primarily from clinical and population-based studies suggest that up to 89% of all adults with ADHD suffer from a psychiatric comorbidity during their lifetime<sup>16</sup>, and that the comorbidity of SUD in adolescents and adults with ADHD might range from 16%–79%<sup>16,21-23</sup>. The heterogeneity of these data is also reflected in research focused on the association between specific ADHD subtypes and SUDs. While some authors find no evidence of

such an association, others have concluded that the hyperactive-impulsive subgroup is more likely to suffer from a comorbid SUD than is the inattentive subgroup<sup>15,22,24</sup>.

To our knowledge, few studies have reported on the relationship between ADHD subtypes and SUD in adult samples. Furthermore, the limited data available stems primarily from America, while the few European studies focused on several comorbid factors, not solely on SUD<sup>16,25</sup>. The purpose of this study was therefore to characterize a clinical sample of adults with ADHD and to identify possible associations between ADHD subtypes, lifetime substance use, and preferences for specific substances.

## Methods

### Sample

Out of all consecutive referrals to the ADHD consultation service of the Zurich University Psychiatric Hospital<sup>26</sup> between 2002 and 2011, we included adults with a confirmed diagnosis of ADHD and with available information on substance use (N=413). There were no other inclusion or exclusion criteria.

### Assessment of ADHD symptomatology

The diagnosis of ADHD was based on the Utah criteria for diagnostic assessment with the Wender Reimherr Interview (WRI)<sup>27</sup>, and translated into German and validated for the German language by Rösler *et al.* and Retz-Junginger *et al.*<sup>28-30</sup>. The Wender-Reimherr Interview is the German version of the American Wender-Reimherr Adult Attention Deficits Disorders Scale (WRAADDSS) for the assessment of adult ADHD. It allows a diagnosis of adult ADHD to be made. It contains seven scales for: attention difficulties, persistent motor hyperactivity, temper, affective lability, emotional overreactivity, disorganization, and impulsivity. Each scale is represented by 3–5 items. A sum score is formed per scale, and each scale has a diagnostic threshold. A diagnosis requires that sum scores for scales 1–2 must each exceed their threshold, and that for scales 3–7, 2 out of 5 sum scores must exceed their threshold. According to DSM-IV Text Revision (TR)<sup>31</sup> specifications, three ADHD subtypes were identified: a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype. Subtypes were derived from the Attention Deficit-/Hyperactivity Self-Report Scale (ADHS-SB) questionnaire (see [Supplementary material](#)). The ADHS-SB is a self-rating instrument for the assessment of adult ADHD in German. It consists of 18 symptoms of ADHD derived from the DSM-IV and ICD-10 criteria for ADHD. The degree of endorsement is rated on four levels: 0 = not at all, 1 = slightly, 2 = moderately, and 3 = severely. The total score is obtained by summing up the 18 individual item scores. Subtype scores were obtained by first summing the respective items (items 1–9 for “inattentive”, items 10–18 for “hyperactive-impulsive”). Then, a cut-off value of 6 had to be exceeded in order for the respective subtype to be assigned. Subjects exceeding the threshold for both the inattentive and hyperactive-impulsive type were assigned to the combined subtype. Note that not all subjects fulfilled subtype criteria. The total number of subjects with a subtype assignment was 327. As reported elsewhere<sup>32</sup>, patients also received a number of questionnaires, including German versions of the Symptom Check List 90-Revised (SCL-90-R)<sup>33</sup>, the Wender Utah Rating Scale

(WURS-k)<sup>28</sup>, and the ADHS-SB<sup>34</sup>. If patients did not answer all questions on the questionnaire items, they were approached again and asked to supply the missing information. When patients had difficulty answering a question, their therapist helped to clarify it and enable them to provide an answer. In addition, third-party information was sought from family members, spouses, school reports, and childhood medical reports to support the diagnostic procedure.

### Assessment of substance use and comorbidity

Assessment of substance use was based on ICD-10 criteria (F10-F19)<sup>9</sup>. Subjects reported on the lifetime use of alcohol, opioids, cannabinoids, sedatives, cocaine, (non-cocaine) stimulants, hallucinogens, and tobacco. ICD-10 criteria were applied by a highly experienced clinician (DE) in a semi-structured interview. No official instrument was used. Substance use was differentiated into abuse/dependence and sub-threshold, i.e. non-dependent and non-abusive, but more-than-singular, use. Comorbid disorders were diagnosed according to ICD-10 by DE in a semi-structured interview, again without an official instrument.

### Statistical analysis

Fisher's exact tests were used to compare frequency of substance abuse/dependence and comorbidity rates between ADHD subtypes, since small cell sizes were frequent. Kruskal-Wallis tests were used to compare questionnaire scores. Bonferroni correction was applied to all substance-related significance tests. A total of 26 tests were conducted, resulting in a Bonferroni-corrected significance threshold of  $p \leq .002$ . P-values surviving this threshold are printed in boldface in the results section. The study has low power: assuming a power of 80%, the minimal detectable difference in substance use frequency among subtypes is between 25–36%, while the power to detect a difference of 10% ranges from 28–48%. Analyses were carried out in Stata 11.2 and Stata 13.1<sup>35</sup>.

### Ethical framework

Authorization by the local ethics committee (Cantonal Ethics Committee Zurich; Kantonale Ethik Kommission Zürich (KEK)) was obtained before the study was conducted (04/2005). All participants received a written description of the study procedure and signed a consent form.

### Results

A total of 64 subjects had no questionnaire data whatsoever and were dropped from further analysis. These “drop-outs” were compared with the remaining 349 subjects and found not to differ in age and gender distribution. Drop-outs more often had affective disorders (24.9% vs. 12.7%,  $p=.05$ ). They tended to have less overall substance abuse or dependence (14.1% vs. 27.8%,  $p=.02$ ). Total substance use excluding abuse and dependence was clearly lower in drop-outs (23.4% vs. 63.6%,  $p=.000$ ).

The average age of the included sample was 38.7 years ( $SD = 11.28$ ), with a gender distribution that was 56% male and 44% female. Other than substance use, the most common comorbidities included affective disorders (25%); neurotic, stress-related and somatoform disorders (15%); and personality disorders (6%).

In the sample with questionnaire data ( $N=332-345$ , depending on questionnaire participants reached average test scores of 35.4 ( $SD=14.51$ ) on WURS-k, 28.5 ( $SD=9.77$ ) on ADHS-SB and 17.6 ( $SD=7.87$ ) on the newly developed SCL-ADHD scale<sup>18</sup>. A total of 233 subjects were identified as belonging to the combined subtype of ADHD (test scores: ADHS-SB 32.9 [ $SD=7.69$ ], WURS-k 37.5 [ $SD=13.91$ ], SCL-ADHD 19.4 [ $SD=7.62$ ]), 70 belonged to the predominantly inattentive type (test scores: ADHS-SB 20.7 [ $SD=5.57$ ], WURS-k 30.1 [ $SD=13.59$ ], SCL-ADHD 14.2 [ $SD=6.52$ ]), and 24 belonged to the predominantly hyperactive-impulsive type (test scores: ADHS-SB 23.9 [ $SD=6.68$ ], WURS-k 40.8 [ $SD=16.16$ ], SCL-ADHD 16.4 [ $SD=7.28$ ]). WURS-k ( $p<.04$ ) and ADHS-SB ( $p<.0001$ ) scores were different between inattentive and hyperactive-impulsive subtypes, while all scores were different at  $p<.004$  for the comparison of inattentive vs. combined subtype.

According to ICD-10 F1x, 26% of all participants at the time of the study, regardless of subtype, fulfilled the criteria for abuse of or dependence on psychotropic substances other than nicotine. The most frequently misused substances consisted of alcohol (8.9%), opioids (6.0%), cannabinoids (8.3%), and cocaine (8.0%). Nicotine abuse/dependence was found in 20.3% of participants.

Subtype-specific analyses revealed that 36.9% of the combined subgroup, 44.3% of the predominantly inattentive subgroup, and 41.7% of the hyperactive-impulsive subgroup currently suffered from a comorbid psychiatric disorder. Additionally, 31.3% of the combined-type individuals, 15.7% of the predominantly inattentive subjects and 41.7% of hyperactive-impulsive patients were diagnosed with abuse or dependence on a psychotropic substance other than nicotine. **Table 1** summarizes the results.

### Discussion

The present study investigated associations between the combined and predominantly inattentive subtypes of adults with ADHD and lifetime substance use, within a clinical sample. The most clinically significant result is the finding that the inattentive subtype showed a statistically significantly smaller rate of cocaine abuse/dependence compared to the combined subtype.

These results are in line with earlier work by Sobanski *et al.*, who had characterized a sample of 118 adults with ADHD and found that the combined type suffered significantly more from lifetime SUDs (48.4%) than did patients with a predominantly inattentive type (23.3%)<sup>16</sup>. On the other hand, our findings contrast with results published by Clure *et al.*, who reported on 43 patients with adult ADHD but found no differences in ADHD subtypes when divided by substance of choice (cocaine, alcohol, and multiple substances)<sup>36</sup>.

The most frequently consumed substance among all study participants was nicotine. This finding is in accord with results from prior studies<sup>37-39</sup>. With regard to subtype-specific differences, some authors have reported that, at least in young adolescents, the inattentive subtype of ADHD is more likely to correlate with higher levels of nicotine use than does the combined subtype<sup>40</sup>. It was suggested that nicotine might primarily improve attention but have less influence on hyperactive-impulsive behavior, which might

**Table 1. Lifetime substance use by ADHD subtype (p-values surviving Bonferroni threshold [ $p \leq .002$ ] in boldface).**

	Inattentive type	Hyperactive-impulsive type <sup>a</sup>	Combined type	p <sup>b</sup> inatt-hyp	p <sup>b</sup> inatt-combined
N	70	24	233		
	%	%	%		
Nicotine abuse/dependence	12.9	12.5	24.9	1.0	.03
Opiates abuse/dependence	1.4	12.5	7.3	.05	.08
Stimulants abuse/dependence	7.1	4.2	9.4	1.0	.64
Alcohol abuse/dependence	1.4	8.3	11.2	.16	.01
Cannabis abuse/dependence	5.7	16.7	8.6	.20	.61
Cocaine abuse/dependence	0	12.5	10.3	.02	<b>.002</b>
Substances total (w/o tobacco) abuse/dependence	15.7	41.7	31.3	.02	.01
Substances total (w/o tobacco) use	57.1	62.5	66.5	.81	.16

<sup>a</sup>Fischer's exact test

inatt-hyp = inattentive vs. hyperactive-impulsive subtype, inatt-combined = inattentive vs combined subtype

explain this finding<sup>41,42</sup>. Other researchers, however, suggest that hyperactive-impulsive symptoms present a greater risk for frequent nicotine use than do inattentive symptoms at a later age, and argue that the relationship between ADHD symptoms and nicotine use might change between adolescence and adulthood<sup>43</sup>.

Our hypothesis that findings would show continuing preferences for the use of specific substances in adulthood according to subtype (beyond cocaine), remains open due to lack of statistical significance. Like earlier reports of (non-cocaine) stimulants being used as self-medication by patients with ADHD, we had also expected to find a higher rate of non-prescribed lifetime stimulant abuse/dependence in the hyperactive-impulsive type, but not in the inattentive one<sup>44,45</sup>. In this sample, however, we found no evidence for this assumption, but lack of statistical power precludes interpreting this as evidence of no difference. We suspect that adults with both hyperactive-impulsive and inattentive symptoms might initially prefer cocaine to stimulants for self-medication, but there is no direct evidence for this assessment<sup>46–48</sup>.

The possibility of using cocaine as an attempt to self-medicate for ADHD symptoms was originally proposed in the early '90s<sup>49,50</sup>. More recently, Saules *et al.* compared the symptom profile among adult ADHD smokers with and without cocaine dependence, and found that when they corrected for the use of nicotine, adults who used cocaine exhibited a more severe adult ADHD symptom profile, as accounted for by the presence of elevated hyperactive-impulsive but not inattentive symptoms. He therefore suggested that cocaine use in smokers with ADHD might be driven by excesses in hyperactivity<sup>50</sup>. Despite differences in sampling, our results are in accord with this finding.

On a different note van Wingen *et al.* investigated structural brain abnormalities in this population and reported of significantly smaller grey matter volumes in the occipital cortex as well as smaller volumes in the putamen in ADHD patients with comorbid cocaine dependence when compared to those without this lifetime diagnosis. The authors of aforementioned study suggested that the differences in putamen volumes may reflect alterations in the availability of striatal dopamine transporters that are available for interaction with methylphenidate, thus giving some explanation for the finding that methylphenidate is less effective in patients with ADHD and a comorbid cocaine dependence<sup>51</sup>.

The main limitation of this study is low power. This means, in particular, that non significant findings cannot be interpreted as evidence of no difference. A further limitation is that our sample was recruited entirely within a university setting, which might contribute to a selection bias. As a result, this clinical sample might have different characteristics than patients would exhibit who are in treatment with a physician in private practice. Nevertheless, the ADHD consultation service of the Psychiatric University Hospital Zurich is the largest institution of its kind in Switzerland and attracts patients from diverse psychosocial backgrounds. Furthermore comorbidities, particularly personality disorders might have confounded the results. For instance, Borderline personality disorder, which often co-occurs with ADHD and is difficult to differentiate, is also known to be associated with SUD<sup>52</sup>. However in this sample that relied for diagnosis of comorbidity on a semi-structured clinical interview, but not on additional instruments, we found only 6% of patients suffering from a comorbid personality disorder. This is low in comparison to some studies reporting prevalence rates between 25 – 78%<sup>53–57</sup>.

In conclusion, our findings underscore the high rate of comorbidity between substance use and ADHD in adults. The more frequent abuse/dependence of cocaine by adult patients with hyperactive-impulsive symptoms should be kept in mind when treating this patient group. Although a limited number of evidence-based treatment strategies currently exist for the concurrent treatment of ADHD and SUD, some studies suggest that stimulant medication remains an efficacious pharmacological treatment option that improves symptoms of ADHD without increasing the likelihood of relapse into SUD<sup>22,58</sup>. Furthermore a study among patients with ADHD and a comorbid cocaine dependence receiving methylphenidate, demonstrated an advantage over placebo with regard to reduction in cocaine use in individuals who responded to ADHD treatment<sup>59,60</sup>.

### Data availability

ZENODO: Dataset 1. Contains all the variables necessary to reproduce the results of Adult attention-deficit/hyperactivity disorder: Associations between subtype and lifetime substance use – a clinical study, Liebrez *et al.*, doi: [10.5281/zenodo.1962361](https://doi.org/10.5281/zenodo.1962361)

ZENODO: Stata source code to reproduce analysis, doi: [10.5281/zenodo.1962262](https://doi.org/10.5281/zenodo.1962262)

### Consent

Written informed consent was obtained from patients.

## Supplementary material

### The ADHS-SB questionnaire (German).

[Click here to access the data.](#)

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### Author contributions

ML, AB and DE conceived the study. AB, ML, AG and DE carried out the research. AG provided statistical expertise and conducted analysis. ML and II prepared the first drafts of the manuscript. All authors contributed to the preparation of the manuscript. All authors were involved in the revision of the draft manuscript.

### Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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# Open Peer Review

Current Referee Status:



Version 1

Referee Report 17 October 2016

doi:10.5256/f1000research.7284.r17021



**Joseph O'Neill**

Division of Child and Adolescent Psychiatry, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA

The investigators determined the effect of ADHD subtype on the prevalence of substance use disorders (SUDs) in a large (413 patients) sample of (medicated?) adult ADHD. In line with expectations, the overall sample evinced high rates of lifetime substance abuse or dependence (26%) and occasional use (57%). The inattentive subtype was significantly less likely to abuse or be dependent on cocaine than the combined subtype. As indicated by the Bordelais reviewers, while not a major advance, this study is a perfect example of normal science in the sense of Kuhn and represents a worthwhile gain in our knowledge of ADHD.

1. The authors list multiple clinical scales used to assess ADHD and state that SUD was assessed based on ICD-10 criteria. Like the Freiburger reviewers, the first question that occurred to me was whether any standardized instrument was administered to assess SUDs?
2. Again, as asked by other reviewers, were the patients in the sample undergoing current pharmacological treatment? Presumably, many were on methylphenidate or other agents.
3. It would be a good idea to cite some statistics for prevalence substance abuse and dependence in the general population around Zürich. Then the reader would have an idea how much higher prevalence is in the adult ADHD clinical sample.
4. The investigators were commendably conservative in claiming significant results, restricting themselves to  $p$ -values  $\leq 0.002$ , based on Bonferroni correction for multiple comparisons. It might be informative to discuss some of the other results that would have been significant under a less stringent cut-off. For example, nicotine abuse/dependence is twice as frequent and alcohol abuse/dependence is nearly ten times as frequent in the Combined as in the Inattentive subgroup. These may be worth commenting on. But I wouldn't discuss any comparisons involving the Hyperactive-Impulsive subgroup, since they are too few (only 24 subjects).
5. In the Introduction, the authors retell the diagnosis and subtyping of ADHD in DSM-III-R, ICD-10, and DSM-IV. They should add a line or two about DSM5, just to round out their brief historical review.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

Referee Report 21 September 2016

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**Swantje Matthies, Eliza Hoxhaj**

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The paper "Adult attention-deficit/hyperactivity disorders: Associations between subtype and lifetime substance use – a clinical study" covers, besides the well-known comorbidity of ADHD with substance use disorders (SUDs), a very interesting field of research concerning the associations between ADHD subtypes and substance use disorders. It adds to the knowledge and differentiates knowledge in focusing on ADHD subtypes. Particularly we noted the large sample size, as it allows more reliable results, the valid assessment of ADHD by using standardized instruments and third-party information and the well detailed statistical analysis. The applied methods appear overall reasonable and valid to us.

We have some remarks that should be addressed:

1. The authors mentioned that assessment of substance use was based on ICD-10 criteria. However they didn't exactly explain their method to gather this data. We noted here the lack of standardized instruments. Furthermore they pooled substance abuse and dependence in one category. The rationale for using this procedure should be given in more detail.
2. We missed information about psychopharmacological treatment. This information might provide potential correlations of treatment/no treatment with substance use.
3. Another question regards the comorbid disorders: It should be discussed that comorbidities, particularly personality disorders might have confounded the results. For instance, Borderline personality disorder, which often co-occurs with ADHD<sup>1</sup> is also known to co-occur with SUD. Further, we wonder that only 6% of the patients had a comorbid personality disorder, which is low in contrast to some studies reporting prevalence rates of personality disorders between 25% and 78% among individuals with ADHD<sup>2-5</sup>. It is also important to make clear, how the authors assessed comorbid disorders. Did they use standardized instruments?
4. The sample size of 327 represented on Table 1, page 4, does not correspond to the described sample size in the paragraph above "Results" ("...were compared with the remaining 349 subjects..." or "N=332-345, depending on questionnaire participants...").
5. In the discussion it might be interesting to explain the use and effects of cocaine among individuals with ADHD, especially with regard to neurobiology. It would also be interesting to know about possible hypotheses and assumptions among the authors concerning the subtype difference in cocaine abuse/dependence. Are there neuropsychological or clinical differences between the subtypes which protect the inattentive subtype from cocaine dependence?
6. The discussion should also comment on the relevance of the presented findings for therapeutic approaches.

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**We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

Author Response 04 Oct 2016

**Michael Liebreuz**, University of Bern, Institute of Legal Medicine, Department of Forensic Psychiatry, Switzerland

We appreciate the dedicated and useful comments of Dr. Swantje and Dr. Hoxhaj and the editor and the chance they gave us to improve the manuscript.

1. The reviewer asks us to elaborate on how ICD-10 criteria for substance use were assessed and why abuse and dependence were pooled.
  1. ICD-10 criteria were applied by a highly experienced clinician (DE) in a semi-structured interview. No official instrument was used.
  2. Estimates of percentages would have been small and noisy if we had separated dependence and abuse. Combining them gives a more robust estimate and seems justified to us also because both describe a serious level of substance use that requires treatment.
2. The reviewer asks for information on psychopharmacological treatment. Unfortunately, such information is not available.
3. The reviewer asks us to discuss and to clarify assessment of comorbidities. We have addressed these questions in the Methods and in the Discussion (Limitations) Section. We now state: *“Comorbid disorders were diagnosed according to ICD-10 by DE in a semi-structured interview, again without an official instrument.”* and *“Furthermore comorbidities, particularly personality disorders might have confounded the results. For instance, Borderline personality disorder, which often co-occurs with ADHD and is difficult to differentiate, is also known to be associated with SUD. However in this sample that relied*

*for diagnosis of comorbidity on a semi-structured clinical interview, but not on additional instruments, we found only 6% of patients suffering from a comorbid personality disorder. This is low in comparison to some studies reporting prevalence rates between 25 – 78%.”*

4. The N=327 reflects the fact that not all patients diagnosed with ADHD fulfilled subtype criteria. Remember that in this study, ADHD was diagnosed according to Utah (Wender-Rheimherr), not DSM, criteria, and subtypes were constructed post-hoc using scores on the ADHS-SB questionnaire. This means that the diagnosis itself does not necessarily entail a subtype assignment, and vice versa. Thus, in about 20 participants ADHS-SB scores were not high enough to yield a subtype classification. This is now explained in the methods section under the heading "Assessment of ADHD symptomatology".
5. The reviewer suggests to discuss the use and effects of cocaine among individuals with ADHD, especially with regard to neurobiology. We have addressed these aspects in an expanded discussion section. We now state: *“On a different note van Wingen et al investigated structural brain abnormalities in this population and reported of significantly smaller grey matter volumes in the occipital cortex as well as smaller volumes in the putamen in ADHD patients with comorbid cocaine dependence when compared to those without this lifetime diagnosis. The authors of aforementioned study suggested that the differences in putamen volumes may reflect alterations in the availability of striatal dopamine transporters that are available for interaction with methylphenidate, thus giving some explanation for the finding that methylphenidate is less effective in patients with ADHD and a comorbid cocaine dependence.”*
6. The reviewer asks us to comment on the relevance of the presented findings for therapeutic approaches. We now point towards research by Levin et al and have expanded the conclusion section: *“Furthermore a study among patients with ADHD and a comorbid cocaine dependence receiving methylphenidate, demonstrated an advantage over placebo with regard to reduction in cocaine use in individuals who responded to ADHD treatment.”*

**Competing Interests:** None.

Referee Report 17 February 2016

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**Marc Auriacombe<sup>1,2</sup>, Jean-Marc Alexandre<sup>2,1</sup>, Melina Fatseas<sup>2,1</sup>**

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In this clinical study, Liebrez *et al.* addressed the association between Adult attention-deficit/hyperactivity disorder (ADHD) subtypes and lifetime substance-use disorders (SUD). This topic is of particular interest (Fatseas *et al.* 2012), as there is a strong literature supporting a relationship between ADHD and SUD (Wilens 2004). An emerging issue is the relationship between SUD and ADHD subtypes (Inattentive, Hyperactive-Impulsive, and Combined). For instance, Tamm *et al.* found more severe SUDs for the Combined subtype (Tamm *et al.* 2012). Our team suggested that Combined and Inattentive subtypes might be associated with more severe addictive disorders (Hurmic *et al.*, CPDD annual meeting 2015). As stated in the manuscript, other authors reported the Hyperactive-impulsive subtype more likely to be associated to a comorbid SUD, or no difference. Data remains limited and this

topic is still in debate.

In this perspective, Liebrez *et al.* conducted a cross sectional study with validated questionnaires assessing ADHD symptomatology and substance use, among 413 adults diagnosed with ADHD. They hypothesized that results would show statistical differences of lifetime SUD prevalence for specific substances, according to ADHD subtype. The main finding of this study was that the Inattentive ADHD subtype was significantly less associated than the Combined subtype to lifetime cocaine abuse/dependence (there was no difference for other substances). However, Hyperactive-impulsive and Inattentive subtypes were not statistically different for their association to any substance disorder.

Liebrez *et al.*'s work is a significant contribution – but not a breakthrough – to research on the relationships of ADHD subtypes and addiction. As reviewers, we noted the clarity of their manuscript, the justification of the study and the definition of their purpose in the introduction section. The method seemed valid to us and missing data (64 subjects) were correctly managed. However, we think that the strategy of analysis should have been more detailed in a specific paragraph. For instance, the usefulness of the WURS-K questionnaire is not explained. The Wender Reimherr Interview (WRI) and the Attention Deficit-/Hyperactivity Self-Report Scale (ADHS-SB) would also have deserved a short presentation and explanation of their use in this study. Another point to argue is the choice of the WRI to diagnose ADHD, as Rosler *et al.* (2006) stated that “on the basis of the WRI, DSM-IV diagnoses cannot be made”, even if “considerable amount of overlap exists” (Rosler *et al.* 2006).

Results are presented and discussed appropriately. The authors mentioned that assessment of substance use was based on ICD-10 criteria. However, for their analysis they pooled substance abuse and dependence in one category without giving the rationale for that choice. In ICD-10 and DSM-IV these are distinct entities. However, in DSM 5 these distinct categories have been combined with other adjustments into one unique category (Hasin *et al* 2013). The authors might clarify this use of ICD-10 in a DSM 5 perspective. The ICD-10 substance use categories might have allowed a more specific study of the association of addiction and ADHD-subtypes?

The absence of statistical difference between Hyperactive-impulsive and Inattentive subtypes for association with any substance disorder was unexpected, especially for stimulants. Liebrez *et al.* discussed the lack of statistical power of their study, which could explain the lack of significant differences. Thus, the hypothesis of a link between specific SUDs and specific ADHD subtypes remains open.

In conclusion, the study of Liebrez *et al.* illustrates the high rate of comorbidity between substance use disorders and ADHD in adults, and reports a specific relationship between cocaine disorder and ADHD Combined subtype. Further research with more statistical power may highlight other specificities of ADHD subtypes in the field of addiction.

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**We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

Author Response 04 Oct 2016

**Michael Liebreuz**, University of Bern, Institute of Legal Medicine, Department of Forensic Psychiatry, Switzerland

We appreciate the time and effort of Dr. Auriacombe, Dr. Alexandre and Dr. Fatseas and respond to their concerns below:

1. The reviewers ask us to explain the usefulness of the WURS-K questionnaire. The WURS-k retrospectively assesses symptoms of ADHD in childhood and as such is part of the diagnostic process for adult ADHD. It is mentioned here for completeness, not because it was a target of analysis.

2. The reviewers ask for more detailed presentations of the Wender Reimherr Interview (WRI) and the Attention Deficit-/Hyperactivity Self-Report Scale (ADHS-SB). We have now added the following two paragraphs on these tests:

WRI: "The Wender-Reimherr Interview is the German version of the American Wender-Reimherr Adult Attention Deficits Disorders Scale (WRAADDS) for the assessment of adult ADHD. It allows a diagnosis of adult ADHD to be made. It contains seven scales for: attention difficulties, persistent motor hyperactivity, temper, affective lability, emotional overreactivity, disorganization, and impulsivity. Each scale is represented by 3–5 items. A sum score is formed per scale, and each scale has a diagnostic threshold. A diagnosis requires that sum scores for scales 1–2 must each exceed their threshold, and that for scales 3–7, 2 out of 5 sum scores must exceed their threshold."

ADHS-SB: "The ADHS-SB is a self-rating instrument for the assessment of adult ADHD in German. It consists of 18 symptoms of ADHD derived from the DSM-IV and ICD-10 criteria for ADHD. The degree of endorsement is rated on four levels: 0 = not at all, 1 = slightly, 2 = moderately, and 3 = severely. The total score is obtained by summing up the 18 individual item scores. Subsyndrome scores for "attention deficit", "hyperactivity", and "impulsivity" can also be obtained."

3. The reviewers question the choice of the WRI to diagnose ADHD, stating that according to Rosler et al. (2006), DSM-IV diagnoses cannot be made based on the WRI. This is true. However, the DSM-IV does not contain a specific diagnosis for *adult* ADHD, while the WRI is specifically

targeted to adults. As Rosler also states "the question remains whether the DSM-IV criteria are adequate to characterize adult ADHD" (p. 1/4) and "An advantage of the WRI could be the extended spectrum of adult psychopathology" (p. 1/10). There is certainly room to argue for either diagnostic approach. Reassuringly, as the reviewers also note, the two approaches show considerable overlap.

4. The reviewers ask for the rationale for pooling substance abuse and dependence. The reason is primarily statistical: estimates of percentages would have been small and noisy if we had separated dependence and abuse. Combining them gives a more robust estimate. This also seems justified to us because both abuse and dependence describe a serious level of substance use that requires treatment.

***Competing Interests:*** None

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